REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Claims 18 and 21 are currently being amended.

Claims 22-45 are being added.

Support for new claims particular dideoxynucleosides is provided, for example, in original claim 3. Support for specification of the triple bond in the linker is provided in the specification at p.6, lines 22-23. Support for particular linker lengths is provided in the specification at p.5 line 22-24. Thus, no new matter is added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-13 and 18-45 are now pending in this application.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 3 and 9 under 35 U.S.C. 103(a) as allegedly being obvious over Evangelista et al., 1996, *Anal. Biochem.* 235:89-97. Even though recognizing that Evangelista does not teach a dideoxynucleotide, the Examiner asserted that it would have been prima facie obvious to one having ordinary skill in the art to modify the labeled deoxynucleotide of Evangelista into a dideoxynucleotide. The Examiner further rejected claims 1-3, 9, and 18-21 over Evangelista et al. in view of Tabor et al, U.S. Patent 5,614,365, and also rejected claims 3, 4, and 9 over Evangelista in view of Haralambidis et al, 1987, *Nucl. Acids Res.* 15:4857-4876. Applicant respectfully traverses these rejections.

Preliminarily, Applicant requests that the Examiner note that even if the Examiner were correct concerning how one of ordinary skill in the art would understand Evangelista et al., the reference does not describe or suggest any fluorescently labeled compound in which the deoxynucleotide has a linker attachment to the nucleotide as specified for ddG, ddC, and ddA in claim 3. Thus, Evangelista cannot make obvious any of claims 22-24 and 32-34. In addition, Evangelista does not describe or suggest fluorescently labeled deoxynucleotides in which the linker is 11, 12, 13, 14, ..., 25 atoms in length and which have the linker attached to the base as specified in claim 3, and therefore cannot make obvious any of present claims 27-32. Still further, Evangelista does not describe or suggest any fluorescently labeled deoxynucleotide in which a linker of 16, 17, 18, ..., 25 atoms in length is incorporated, and therefore cannot make obvious claim 43.

More generally, Applicant respectfully requests that the Examiner reconsider the discussion provided in the Amendment filed July 21, 2003 with respect to the understanding of one of ordinary skill in the art of the mention of fluorescently labeled ddNTPs in Evangelista.

Focusing on a few pertinent points, the introductory discussion in Evangelista in which certain uses of fluorescently labeled dNTPs and ddNTPs are cited would be viewed by one of ordinary skill in the art as just that, a background introduction to fluorescently labeled nucleotides, not as suggestions for the use of the particular compounds described in the reference.

Indeed, one of ordinary skill in the art understands the differences in behavior of ddNTPs and dNTPs in incorporation by DNA polymerases, and that different polymerases can have very different behavior for such incorporation. This is clearly recognized in Evangelista, which refers to determining whether a fluor-labeled dNTP is suitable for DNA incorporation due to incompatibility with the DNA polymerase (p.94, col. 1). The other cited references also do not indicate that the present compounds would be particularly useful to resolve band intensity and anomalous migration artifacts in sequencing with such thermostable DNA polymerases. Thus, there was no suggestion from the cited references that advantageous results would be obtained in

sequencing using the present compounds with a thermostable DNA polymerase as specified in claim 1, or a modified such thermostable DNA polymerase as specified in claim 2. Indeed, using labeled ddNTPs with 5 atom linkers with thermostable DNA polymerase and modified thermostable DNA polymerase, variation of as much as 20-fold in band intensity was observed (specification p.3, last paragraph). Likewise, large variations were observed when using AMV reverse transcriptase, even with compounds with 10-atom linkers (p.3, first paragraph). Thus, one of ordinary skill in the art would interpret such results as indicating that high levels of band intensity variation as well as problems with dye induced band compression would be likely to exist when using compounds such as those presently claimed in sequencing.

Despite results such as those described above, Applicant discovered that sets of 4 labeled ddNPTs can be advantageously used in sequencing with thermostable DNA polymerases such as *Taq* DNA polymerase, including modified such polymerases to provide improved band uniformity without dye-induced compression, results which were not suggested by the cited references individually or in the combinations cited by the Examiner. In particular, description of kits in Tabor does not suggest the present kits of claim 1 and dependent claims in the absence of suggestion to use the specified labeled ddNPTs in sequencing.

To the contrary, Evangelista and the other references cited by the Examiner must be interpreted in view of such additional references that had reported high levels of variation. It is well-established that in an obviousness analysis, a reference cannot be taken in isolation separated from other relevant art. Instead, one of ordinary skill in the art would interpret a reference in the context of other available art. Thus, while the dNPTs described in Evangelista were reported to be useful for particular applications, the essentially negative results that had been reported for various labeled ddNPTs in sequencing applications contradicts the Examiner's asserted suggestion from Evangelista to provide the kits of claim 1.

Further, interpreting the cited references appropriately in context demonstrates that Evangelista, neither alone nor in combination with Haralambidis, does not suggest the compounds of claim 3, i.e., cyanine dye labeled dideoxynucleotides with the specified linkers and

linker attachments. As indicated above, interpretation of Evangelista as well as Haralambidis in context with reports of various sequencing results using fluor-labeled ddNPTs demonstrates that the cited references do not suggest making the present claimed cyanine dye labeled dideoxynucleotides.

The lack of suggestion is particularly clear with respect to the compounds specified in new claims 22, 23, and 24 in which specific positional linker attachments for ddG, ddC, and ddA are specified. (Such lack of suggestion also applies to the corresponding claimed kits containing such compounds.)

The lack of suggestion is also particularly clear for labeled dideoxynucleotides generally having linkers in the range of 16-25 atoms in length as specified in claims 32 and 45 (and kit claims 43 and 44).

As an additional note, in connection with the rejection of claim 4 over Evangelista in view of Haralambidis, the Examiner asserted that Haralambidis showed a linker corresponding to the 4^{th} linker in claim 4. Applicant respectfully submits that Haralambidis shows a linker on a deoxynucleotide that has a terminal N, which is not present in the 4^{th} linker of claim 4. Therefore, neither Haralambidis nor Evangelista nor the combination of those references describes or suggests any of the linkers shown in claim 4.

In view of the above discussion and with reconsideration of the discussion presented in the previous amendment, Applicant respectfully requests that the Examiner reconsider and withdraw the present rejections. However, if the Examiner intends to maintain the rejections, Applicant requests that the Examiner consider each of the claim individually, in particular the new claims submitted herein.

Applicant submits that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 15 March 2004

By _____

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